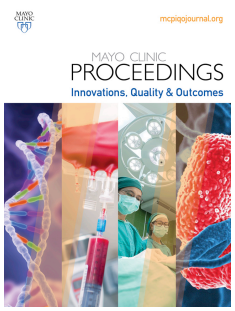
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



Cancer screening during the COVID-19 pandemic: A systematic review and meta-analysis.

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Title Page

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ABSTRACT

Objective: To assess the impact of measures designed to mitigate the spread of COVID-19 on worldwide cancer screening.

Patient and Methods: We systematically searched PubMed.gov, Ovid Medline, the Cochrane COVID-19 study register, ClinicalTrials.gov, and Embase without language restrictions for studies published between January 1, 2021 and February 10, 2021. Studies were selected for full text review which contained data on patients screened for any type of cancer during the COVID-19 pandemic and comparison data from a time interval just prior to the pandemic. Data was obtained through dual extraction. All the included studies were assessed for quality and risk of bias. A meta-analysis was performed on 13 studies: seven on screening mammography; five on colon cancer screening, and three on cervical cancer screening. The screening outcomes were reported as pooled incidence rates ratios using the inverse variance method and random effects models. All studies included in our meta-analysis reported the number of patients screened for cancer in defined time intervals before and during the COVID-19 pandemic.

Results: Incidence rate ratios (IRRs) were significantly lower for screening during the COVID-19 pandemic for breast cancer (0.63, 95% CI=.53,.77,

P=<.001), colon cancer (0.11, 95% CI=.05,.24, *P*=<.001), and cervical cancer (0.10, 95% CI =.04,.24,*P*=< 0.001).

Conclusion: We found moderate level evidence showing significant decreases in cancer screening for breast, colon, and cervical cancers during the COVID-19 pandemic, which may add further morbidity and mortality to this public health crisis.

Abbreviations:

COVID-19: Coronavirus disease of 2019

GRADE: Grading of Recommendations, Assessment, Development and Evidence

Text

INTRODUCTION

In order to call countries into action to reduce transmission of the coronavirus disease of 2019 (COVID-19) among their citizens, the World Health Organization declared this novel viral illness a pandemic on March 11, 2020. Across the world, governments enforced quarantines, asking their citizens to stay home and avoid contact with others because epidemiological studies showed that stay-at-home orders effectively reduced the case rates and hospitalizations associated with the virus.[1,2] While these lockdowns may have led to a reduction in viral transmission, the impacts on public health initiatives such as cancer screening are still being determined. As a result of the new measures to mitigate the spread of COVID-19, routine visits to physicians decreased substantially. Data shows that the number of primary care visits in the United States (US) decreased by 50% in the second quarter (April 1 to June 30) of 2020 compared to average levels from 2018-2019 for this same period of time.[3] Primary care physicians attempted to provide care by implementing telemedicine, which comprised 35% of visits in the second quarter of 2020 compared to 1% of visits in all of 2018-2019.[4] This marked reduction in office visits likely had a significant impact on preventative services, including cancer screening.

In April 2020, the Center for Medicare and Medicaid Services recommended considering postponing non-urgent services, including preventative care visits and screening examinations.[5] This affected ambulatory screenings, including colonoscopies, mammograms,

Papanicolaou smears, and low-dose chest computerized tomography. Modelling studies predict increased rates of tumor upstaging as well as higher disease specific morbidity and mortality due to decreased and delayed cancer screening in 2020.[6,7] The aim of our systematic review was to examine the impact the COVID-19 pandemic has had on worldwide cancer screening or secondary prevention.

METHODS

Search Strategy, Study Selection and Inclusion Criteria

We began our systematic review by writing a study question and protocol (Supplemental Appendix 1) which was registered through PROSPERO (ID: CRD42021241831) on March 11, 2021. Our systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines.[8]

We developed our search strategies, using medical subject heading terms and text words which were selected based on common indexing practices. Search terms were compiled and tested repeatedly to produce sensitive searches to capture potentially relevant publications. We searched the following databases: PubMed.gov; Ovid Medline; the Cochrane COVID-19 study register; ClinicalTrials.gov; and Embase, without language restriction, for studies published between January 1, 2021 and February 10,

2021. Searches were performed employing the following keywords: cancer screening; lung cancer screening; mammography; breast cancer screening; colonoscopy; colon and rectum cancer; cervical cancer screening; Papanicolaou or PAP testing; prostate specific antigen or PSA; prostate cancer screening; COVID-19; Sars-CoV-2; and 2019 novel coronavirus. Our search was augmented by author and reference tracking to identify additional studies.

Included in our analysis were retrospective observational studies of cohorts or cancer registries. We chose studies which included the numbers of screened patient populations both just prior to and during the pandemic (specifically the years of 2019 and 2020). If studies only contained screening rates, we attempted to obtain the absolute numbers of patients screened by contacting the authors for unpublished data. Studies were excluded if these data were not available. Also excluded, were studies which did not record the number of patients screened for any cancers both during the year 2019 and in the pandemic lockdown period of 2020. Abstract only papers were excluded, as study design and methods of data acquisition may not be able to be evaluated and reconciled. We decided by consensus to exclude outlying results in the statistical analysis of our meta-analysis.

Data Collection and Quality Assessment

We collected initial references in citation files (using the software Covidence), removed duplicates, and began our screening process for titles and abstracts against eligibility criteria. Two reviewers (MM and RAS) independently reviewed abstracts for inclusion in the initial screening phase, followed by the full text screening phase of our systematic review. Studies were selected for full text review if they contained data on patients screened for any type of cancer during the COVID-19 pandemic and contained comparison data from a time interval just prior to the pandemic. Disagreements among reviewers in the initial abstract screening phase and full text review were resolved by consensus by two reviewers (MM and RAS). Disagreements among reviewers in the full text screening phase were reconciled by discussion and consensus with a third reviewer (BP).

Two reviewers (MM and RAS) evaluated all selected studies from phase two of screening independently for inclusion in data extraction. Data extracted from studies included study description (research setting), methods used to record screening rates, and comparison data of screening rates before 2019. Two reviewers (MM and RAS) also independently extracted data from the included studies and performed an assessment of the quality and risk of bias of all included studies using the Newcastle-Ottawa Quality Assessment Tool for the Observational, Cohort and Cross-Sectional Studies available from the National Institute of Health.[9] The

quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[10]

Statistical Analysis

A meta-analysis was performed for three outcomes: changes in screening rates for breast cancer; colon cancer; and cervical cancer. Data on lung cancer screening was insufficient to be included in our meta-analysis. The comparison groups were the time periods before and during the COVID-19 pandemic. The screening outcomes were reported as incidence rates, and the pooled effect size reported in this analysis is the incidence rate ratio (IRR). The IRR was calculated from each study using the number of patients screened in time intervals (days) before and after the start of the COVOD-19 pandemic. The individual study IRRs are unadjusted, and both the IRRs and the pooled IRR were calculated using the default assumption form the meta::metainc function in R version 4.9-6. The pooled IRR statistic for breast cancer screening was based on seven studies; data for colon cancer screening was based on five studies; and the analysis of cervical cancer screening was based on three studies. The pooled IRRs were calculated using the inverse variance method and random effects models were presented. Random effects models were used as the intention of our meta-analysis was to generalize the results beyond the included studies given the universality of our data and the heterogeneity of our study of

several patient populations. For consistency, the same model was employed for all three outcomes. Heterogeneity between studies was assessed using the chi squared and I^2 statistic. Leave-one-out analyses were performed to calculate pooled estimates to determine if studies with high influence were impacting the significance of the results.

RESULTS

Our database search and study selection process are outlined in the flow diagram (Figure 1). We identified 748 articles for our systematic review with 113 identified as eligible for full-text review. Eleven of these studies met our inclusion criteria and provided the numbers of patients screened before and after lockdown measures were instituted.[11-21] These studies met inclusion criteria for our meta-analysis with their characteristics described in Table 1.[11-21] We five studies which examined colon cancer screening, seven studies for breast cancer screening, and three for cervical cancer screening in our statistical analysis (Table 1). There were two of our studies which reported on more than one type of cancer screening.[12,14]

The result of pooling studies that tracked breast cancer screening before and during the COVID-19 pandemic found a significantly lower rate of breast cancer screening during the pandemic compared to before with a

pooled incidence risk ratio (IRR) of 0.63 (95% CI=.53,.77, *P*=<.001)(Figure 2). The Gorin 2021 study was removed from this analysis as it was identified as an outlier.[12] Results of leave-one-out influence analyses showed that the significance of the pooled estimate does not change after omitting any of the studies.

The result of pooling the studies assessing colon cancer screening before and during the COVID-19 pandemic found a significantly lower rate of colon cancer screening during the pandemic compared to before (pooled IRR = 0.11, 95% CI=.05,.24, *P*=<.001)(Figure 2). Results of leave-one-out influence analyses showed that the significance of the pooled estimate did not change after omitting any of the studies.

The result of pooling the studies that evaluated cervical cancer screening before and during the COVID-19 pandemic found a significantly lower rate of cervical cancer screening during the pandemic compared to before (pooled IRR = 0.10, 95% CI =.04,.24, *P*=< 0.001)(Figure 2). Results of leave-one-out influence analyses showed that the significance of the pooled estimate does not change after omitting any of the studies.

Since there were only two studies devoted to the evaluation of lung cancer screening during the COVID-19 pandemic, we were unable to perform a meta-analysis on these data.

DISCUSSION

The COVID-19 pandemic has become one of the most widespread challenges to worldwide public health in the last century. The magnitude of disease and mortality associated with this novel disease led to suspension of routine health care, including age-appropriate cancer screening. Our meta-analysis pooled data from 11 studies that assessed cancer screening data from a variety of settings: six on breast cancer, five on colon cancer, and three on cervical cancer (Figure 2). Our analysis demonstrated a significant decrease in the incidence of screening for all three cancer types during the pandemic. Compared to the baseline before the pandemic screening mammography declined to 63% (95% CI =.53,.77, *P*=<.001), screening colonoscopy decreased to 11% (95% CI=.05,.24), and cervical cancer screening diminished to 10% (95% CI=.04, 0.24, *P*=<.001). The greater drop for colonoscopy and cervical cancer screening may be attributable to more invasive screening techniques for these cancers compared to that for breast cancer.

The most concerning potential effect of a decrease in cancer screening is an increase in cancer mortality. Mortality data due to decreased screening during the COVID-19 pandemic is not yet available. The magnitude of a potential increase in mortality will likely add to the global public health burdens of this pandemic. For most of the 20th century, cancer mortality has risen. Overall cancer mortality has decreased every year since 1991,

however, and from 1991 to 2018, cancer mortality decreased by 30%.[22] Screening in the US as of 2018 has been demonstrated to prevent 10,179 breast cancer deaths over the lifetime of a cohort of 50-year-old women, 74,470 colon cancer deaths in the cohort of 50-year-old men and women, and 27,166 cervical cancer deaths in a cohort of 21-year-old women.[23] It seems reasonable to expect an increase in cancer-specific mortality due to the decrease in cancer screening rates; however, in remains unclear to what degree this may occur. The abrupt drop in cancer screening resulting from the lockdowns during the pandemic was unprecedented. Global effects on future cancer mortality due to the pandemic have widespread public health ramifications which are yet to be determined.

Another important feature of our analysis is the demonstration of consistent results across from a wide spectrum of health care settings. We analyzed studies performed in multiple countries, including the US, Italy, Taiwan, the Netherlands, France, and Romania. The data that researchers collected came from a range of sources as well. For instance, some examined hospital records from single or multiple hospitals.[12,21,23,30] Others mined regional or national healthcare databases.[13, 6,17,25,28] One study used data from insurance company claims for screening procedures.[18] Notably, the reported decreases in cancer screening rates were consistently large within each cancer type; the range in the decline of screening mammography rates was 51-77%, screening colonoscopies fell by 1-55%,

and cervical cancer screening was 5-18% of the pre-COVID-19 pandemic rates. The consistency of these results is support for generalizability of our findings across various healthcare settings.

Limitations to our study are reflective of our study design. Our study question could only be answered by collecting and analyzing data from retrospective observational studies of cohorts of patients or data collection from patient registries. Since all of the studies were retrospective and unblinded, the potential exists for a risk of bias in the assessment of outcomes and data reporting (Table 2). However, since the outcomes are highly objective, we assess the risk of reporting or selection bias to be low. None of the studies included a method for ensuring any patients were not counted more than once in the data registries. The certainly of evidence was evaluated with the GRADE approach for all three of our studied outcomes.[10] Using this approach, we determined the quality of evidence to be high for diminished colon cancer screening and moderate for the diminution of breast and cervical cancer screening during the beginning of the COVID-19 pandemic. We reviewed several studies which reported only the rates in which cancer screening was reduced during the pandemic.[7,24-30] Without data on the numbers of patients screened we were unable to include these studies in our statistical analysis. In an attempt to collect more data we contacted the corresponding authors of these studies twice and received data from only one, which became an included study.[21] Bias due to

confounding seems unlikely in our studies, although covariate analysis was not performed in any of our included studies and an inference cannot be made regarding screening disparities (Table 2). Including data from an insurance registry is a potential confounder for two of our included studies.[12,21] The short time period of diminished screening for cancer during the COVID-19 pandemic lock-down periods has unclear long-term implications.

In conclusion, we found high quality evidence for diminished screening of colon cancer and moderate quality of evidence for diminished screening of both breast and cervical cancers across a spectrum of healthcare systems in several different countries during the COVID -19 pandemic. With current cases of COVID-19 in the hundreds of millions worldwide, the complete public health ramifications of this novel viral illness remain to be fully understood and elucidated. The effects of the pandemic will likely be lengthy and manifest in changing the epidemiology of many concomitant disease processes. A downstream result of the pandemic may be an increased incidence of advanced stage tumors as well as a rise in cancer-specific mortality.

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Legends for Tables: Table 1. Study characteristics

Table 2. Quality assessment and risk of bias

Legends for figures: Figure 1. PRISMA flow diagram

Figure 2. Outcomes Measues

Table 1. Study characteristics

Breast Cancer

Author, year	**Setting and database**	**Study design**	**Screening method**	**Pre-COVID-19 pandemic study interval (days)**	**Covid-19 pandemic study interval (days)**
Mantellini 2020[14]	Italy, National Database (20/21 regions reporting)	Retrospective observational study	Mammography	151	152

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Sutherland 2020[15]	New South Wales, Australia, multiple databases	Retrospective observational study	Mammography	122	122
Chou 2020[16]	Taiwan, public academic hospital electronic records	Retrospective observational study	Mammography	154	154
Tsai HJ 2020[17]	Taiwan, Kaohsiung City Community Hospital	Retrospective observational Study	Mammography	59	60
Song 2020[18]	Database from 34 US states from insurance claims data	Retrospective observational study	Mammography	800	149
Tsai HY 2020[19]	Taiwan National screening database	Retrospective observational study	Mammography	119	120

Colon cancer screening

Author, year	Setting and database	Study design	Screening method	Pre-COVID-19 pandemic study interval (days)	Covid-19 pandemic study interval (days)
Challine, 2021[11]	France, National database	Retrospective observational study	Colonoscopy	75	58
Gorin 2021[12]	University of Michigan, US, ambulatory medicine clinics	Retrospective observational study	Colonoscopy	52	52

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Latinga 2021[13]	Netherlands, multi-center database	Retrospective observational study	Colonoscopy	62	62
Mantellini 2020[14]	Italy, National database (20/21 regions reporting)	Retrospective observational study	Colonoscopy	151	152
Chiriac 2021[20]	Romania, St. Spiridon Emergency Hospital electronic records	Retrospective observational study	Colonoscopy	199	199

Cervical Cancer

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Author, year	Setting and database	Study design	Screening method	Pre-COVID-19 pandemic study interval (days)	Covid-19 pandemic study interval (days)
Gorin 2021[12]	University of Michigan, US, ambulatory medicine clinic	Retrospective observational study	Cervical cytology (Papanicolaou testing) and HPV testing	52	52
Mantellini 2020[14]	Italy, 20/21 regions database	Retrospective observational study	Cervical cytology (Papanicolaou testing)	151	152
Miller 2021[20]	Southern California, Integrated health care system	Retrospective observational study	Cervical cytology (Papanicolaou testing) and/or HPV testing	78	85

Table 2. Modified Newcastle-Ottawa quality assessment score[a]

Study	**Selection**		**Comparability**	**Outcome**
	Representativeness of exposed cohort	Ascertainment of exposure		
Challine, 2021[11]	1	1	1	1
Gorin, 2021[12]	1	1	0	1
Latinga, 2021[13]	1	1	0	1
Mantellini, 2020[14]	1	1	1	1
Sutherland, 2020[15]	1	1	0	1
Chou, 2020[16]	1	1	0	1
Tsai HJ, 2020[17]	1	1	1	1

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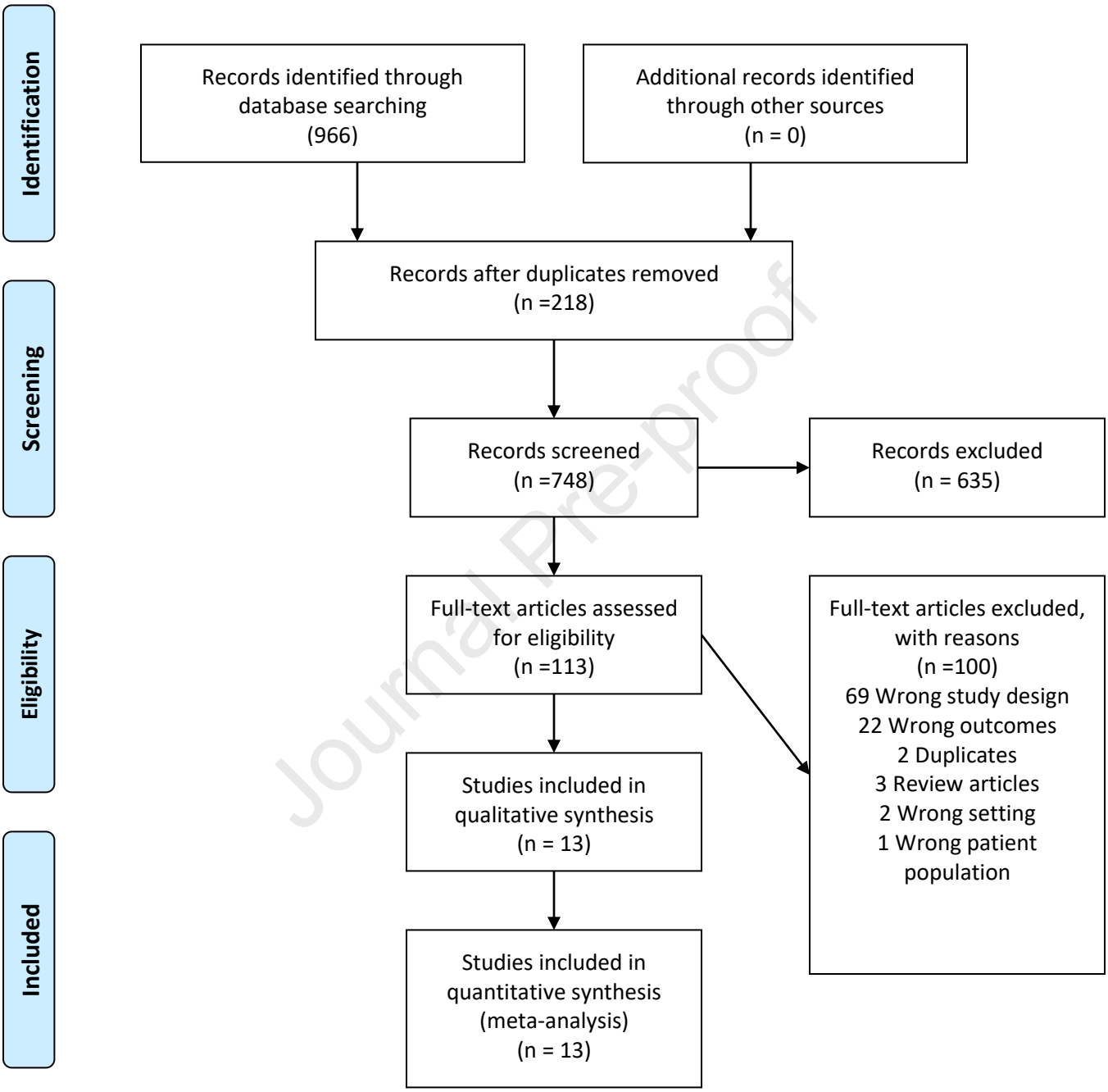
Song, 2020[18]	1	1	1	1
Tsai HY, 2020[19]	1	1	1	1
Chiriac, 2021[20]	1	1	1	1
Miller, 2021[21]	1	1	0	1

[a)] A score of 1 is equal to 1 star and signifies a low risk of bias

Figure 1. Prisma Flow Diagram



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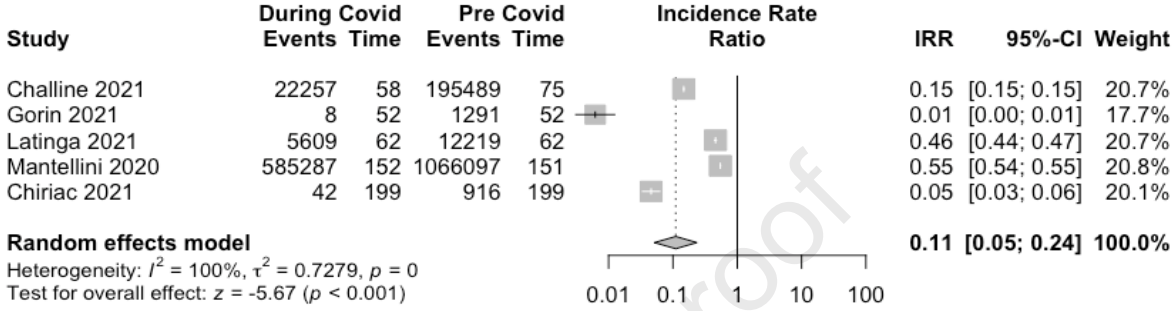
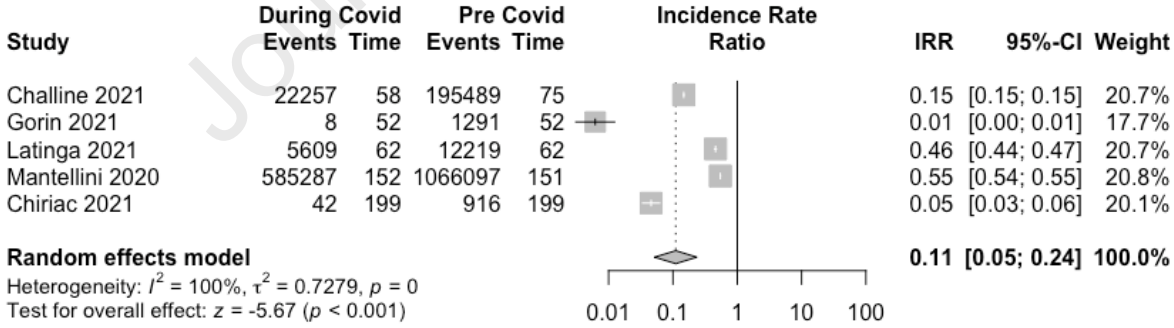
For more information, visit www.prisma-statement.org.

Figure 2. Outcomes measures

Breast Cancer Screening Forest Plot



Colon Cancer Screening Forest Plot



Cervical Cancer Screening Forest Plot